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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/801,078	03/15/2004	Krzysztof Palczewski	029060-000200US	9475

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EXAMINER	
HUANG, GIGI GEORGIANA	
ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
12/02/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/801,078	PALCZEWSKI ET AL.	
	Examiner	Art Unit	
	GIGI HUANG	1617	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 19 November 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *52 and 54-62*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Zohreh A Fay/
Primary Examiner, Art Unit 1627

Continuation of 11. does NOT place the application in condition for allowance because: The amendments while overcoming the 112 rejections of record and the provisional double patenting rejection of record; do not overcome the art rejections of record.

Claims 53, 63-71 are cancelled and moot.

Wherein after amendment:

Claims 52, 54, 60,62 currently stand rejected under 35 U.S.C. 103(a) as being unpatentable over Chapple et al. (Looking at protein misfolding neurodegenerative disease through retinitis pigmentosa) in view of Asato et al. (Fluorinated Rhodopsin Analogues from 10-Fluoro- and 14-Fluororetinal);
Claim 55 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Chapple et al. (Looking at protein misfolding neurodegenerative disease through retinitis pigmentosa) in view of Asato et al. (Fluorinated Rhodopsin Analogues from 10-Fluoro- and 14-Fluororetinal) as applied above, in view of Grant et al. (Treatable forms of Retinitis Pigmentosa Associated with Systemic Neurological Disorders-Abstract); and
Claims 56-59, 61 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Chapple et al. (Looking at protein misfolding neurodegenerative disease through retinitis pigmentosa) in view of Asato et al. (Fluorinated Rhodopsin Analogues from 10-Fluoro- and 14-Fluororetinal) as applied above, in view of Lang (Ocular drug delivery conventional ocular formulations) and Geroski et al. (Drug Delivery for Posterior Segment Eye Disease).

Applicant's arguments in regards to Chapple in view of Asato are directed to the assertion that Chapple does not describe an actual in vivo use in human patients, only in vitro observations and a lack of in vivo data. This is fully considered but not persuasive as Chapple et al is implicitly if not explictly addressing human patients with autosomal dominant retinitis pigmentosa including that from the P23H mutation as he recites that retinitis pigmentosa is the most common cause of inheritied blindness estimated to affect one in every 4000 individuals (first page, first column first paragraph which is implicitly/explicitly addressing human individuals/patients), states that the review is focused on the most prevalent from of retinitis pigmentosa, autosomal dominant retinitis pigmentosa (first page, second column, second paragaph), also teaches that the most frequent rhodopsin mutations that form this inheritied condition(which is implicitly/explicitly human individuals/patients) is the proline to histidine change- P23H (first page, second column fourth paragraph). Chapple also addresses that cytoplasmic chaperones can influence the folding and pocessing of rhodopsin in both wild type and P23H rhodopsin (second page, second column second paragraph); and that the addition of 9-cis retinal to culture expressing P23H mutation improved the opsin mutant opsin allowing improved movement of opsin to reach the plasma membrane, whereby the retinoid can be used as a 'chemical' chaperone to stabilize the folding of the mutant opsins shifting the equilibrium toward functional proteins (second page, first column last paragraph-second column first paragraph). Chapple teaches that is known in the art that Vitamin A has some therapeutic value in retinitis pigmentosa. Chapple also teaches that while the trial was not focused on patients with the these misfolded mutations (implicitly/explicitly the same patients addressed throughout the article-humans), Chapple states "if they had been the clinical outcomes may have been even better" and that further investigation of these methods may lead to therapies for the misfolded protein disease and other conditions. As a result, Chapple is clear on the use of 9-cis retinal for the P23H mutation of retinitis pigementosa (autosomal dominant retinitis pigmentosa) with a reasonable expection of success contrary to the assertion that there is no description of in vivo use in human patients. The argument that Chapple does not have in vivo data and there is a burden of establishing that the in vitro observations would be reasonably expected to occur in vivo is not persuasive as Chapple as addressed above (see full document, specifically areas cited above) states that while the trial was not focused on patients with these mutations, but that "if they had been the clinical outcomes may have been even better" and that further investigation of these methods may lead to therapies for the misfolded protein disease and other conditions wherein Chapple establishes a reasonable expectation of success for treating a patient with the 9-cis retinal for the condition (in vivo). In regards to Applicant's assertion that Asato is directed to wildtype opsin and not P23H opsin and prevent its aggregation in vivo. This is fully considered but not persuasive as it is not commensurate in scope with the claims as written and Applicant's own specification does not have a human patient example or a demonstration of the in vivo aggregate folding currently argued, but nevertheless Chapple already has established the use of 9-cis retinal for P23H autosomal dominant retinits pigmentosa which does to the improved folding and transportation of the 9-cis retinal for treating the P23H autosomal dominant retinitis pigmentosa and addressed its beneficial use in patients with the condition, encompassing the issue of the aggreates (treatment of the condition addresses the aggreates) as the adminstration of the compound (e.g. 9-cis retinal, 9-cis-10F-retinal as addressed with Asato) intrinsically will have the same effect. Asato is presented to show the known substitiution of fluorine on 9-cis retinal to form analgoues and that certain forms such as the 10-fluororetinal behaves very similarly to the parent retinal in all isomers, such as the 9-cis retinal, except for the all-trans and 13-cis form, to yield stable pigments (demonstrating functional equivalence of the 9-cis 10-fluorinated retinal analog to the parent 9-cis retinal). Asato also addresses that this is not unexpected as the fluorine atom does not have a significant effect on pigment formation (does not hinder) as sterically, it is not significantly larger than hydrogen (expected functional substitution to yield expected functional equivalence). As a result, Asato demonstrates that 9-cis retinal and its analog: 9-cis-10F-retinal are functional equivalents wherein it is well within the skill of one in the art to substitiute one functionally equivalent retinal for another with a reasonable expectation of success. Additionally, Chapple addresses that chaperones can be utilized to manipulate the folding of normal (wild type) and mutant rhodopsin wherein there is an express teaching for chaperones for both normal (wild-type) and mutant rhodopsin with a reasonable expectation of success; and Chapple addresses the use of 9-cis retinal as a chaperone. As a result, the use of a functional equivalent such as its analog: 9-cis-10-F-retinal as addressed by Asato for the same purpose as taught by Chapple would have a reasonable expectation of success. It is noted that Applicant's use of the term "wild type" is confusing as the term has various meanings depending the on the context but is traditionally viewed as to be synomous with "normal" and is currently taken as such (normal rhodopsin/opsin) based on its application to Asato. Applicant's argument that the steric similarity of hydrogen and fluorine is significant as the electronegativities shift the character of the base 9-cis retinal and the shiift toward the fluorine cannot be assumed to have insignificant effects on the 9-cis double bond or the retinal as a whole. This is fully considered but not persuasive as Asato had

demonstrated that the substitution of the fluorine on the 14 position yielded a retinal that could not form a stable pigment, but the substitution of the fluorine in the 10 position of the 9-cis retinal did not affect its function and in fact performed similarly to the parent 9-cis retinal demonstrating that this analog and the parent 9-cis retinal are functionally equivalent wherein the subtitiution of the 9-cis 10-F-retinal for the 9-cis retinal has a reasonable expection of success. The rejection is maintained.

In regards to Chapple et al. in view of Asato in view of Grant et al., Applicant's arguments are directed to Chapple in view of Asato which is addressed above. The rejection is maintained.

In regards to Chapple et al. in view of Asato in view of Lang and Geroski et al., Applicant's arguments are directed to Chapple in view of Asato which is addressed above.The rejection is maintained.